Remarks

I. Status Of The Claims And Support For The Amendment

Claims 1-13, 23-36, 39, 56 and 58 have been canceled without prejudice to or disclaimer of the subject matter therein. Applicants reserve the right to file one or more continuing applications with claims directed to the canceled subject matter.

New claim 72 has been added.

Claims 14-22, 37, 38, 40-55, 57 and 59-72 are pending in the application, with claims 14, 22, 52, 53, 57 and 62 being the independent claims.

Support for the amendment of claim 37 is found in the Specification, for example, at page 31, line 4.

Support for new claim 72 is found in the Specification, for example, at page 28, line 6.

The dependency of each of claims 37, 43-45, 65-68 and 71 has been amended.

No new matter has been added by these amendments, and their entry is respectively requested.

II. The Rejection Under 35 U.S.C. § 103 Should Be Withdrawn

At page 2 of the Office Action, the Examiner rejected claims 1-18, 21, 22, 23, 26-28, 30-36, 39-43, 47-51, 66-68 and 71 under 35 U.S.C. § 103(a) as allegedly being obvious over Rewinkel *et al.*, *Curr. Pharm. Design* 5: 1043-1075 (1999) (hereinafter "Rewinkel"), in view of de Nanteuil *et al.*, U.S. Patent No. 5,814,622 (hereinafter "de Nanteuil") and in further view of Adams *et al.*, U.S. Patent No. 5,780,454 (hereinafter "Adams").

Applicants respectfully traverse this rejection. A *prima facie* case of obviousness has not been established. Even if, *inter alia*, a *prima facie* case of obviousness had been established, it is rebutted by the surprising results provided by the claimed invention.

Briefly, the Examiner asserts at pages 2-3 of the Office Action (1) that Rewinkel discloses compound of formula 21 (page 1052, Table 3), which is a boronic acid having a methoxyalkyl substituent for R9 in present claim 1, a proline amino acid residue as recited in claim 17, a hydrophobic moiety in the form of a diphenylalanine residue, a protected N-terminal amine, and a thrombin inhibition Ki of 14 nM; (2) that de Nanteuil discloses organoboronic acids and pharmaceutically acceptable salts thereof; and (3) that Adams discloses pharmaceutically acceptable base addition salts, including alkaline metal salts, alkaline earth metal salts, and amine salts.

At page 4 of the Office Action, the Examiner provided an argument for alleged motivation to make the claimed base addition salts. The Examiner cited *In re Williams*, 89 U.S.P.Q. 396 (CCPA 1951), for the proposition that it would have been obvious to form salts from known acids. At page 4 of the Office Action, the Examiner also cited Davies *et al.*, *The Pharmaceutical Journal 266*: 322-323 (2001) (hereinafter "Davies"), for the proposition that one of ordinary skill in the art would have made a salt of a known acid, *e.g.*, compound 21 of Rewinkel, in order to alter the permeability, solubility or other physiological properties commonly associated with producing pharmaceutically acceptable salts. The Examiner also stated that "[de Nanteuil] describe pharmaceutically acceptable salts of organoboronic acids and thus provide an expectation of success for performing the said modification." Office Action at page 4. The Examiner also stated that Adams discusses that "[p]harmaceutically acceptable salts of organoboronic acid

salts [sic] include alkaline metal salts, alkaline earth metal salts (including calcium) and amine salts." *Id.*

Applicants respectfully disagree with these conclusions and the reasoning upon which they are based. Applicants reiterate their arguments already of record, subject to the clarifications provided in the amendment and reply filed September 26, 2007, the evidence of record, and the Declaration by Dr. Kennedy filed September 26, 2007 ("the Kennedy Declaration"). Moreover, Applicants provide herewith a Declaration Under 37 C.F.R. § 1.132 by Dr. Stephen Phillip Marsden ("the Marsden Declaration"). Applicants also provide the following additional comments with respect to this rejection.

At page 5 of the Office Action, the Examiner dismisses Applicants' previous arguments regarding Wu *et al.*, *J. Pharm. Sci 89*: 758 (2000) (hereinafter "Wu"), which is of record in the present application, which Applicants discussed in detail in the Supplemental Amendment and Reply filed September 26, 2007, and which Dr. Kennedy discussed in his Declaration.

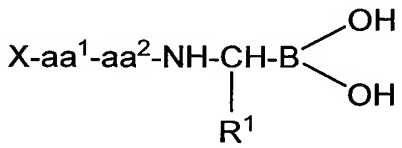
Specifically, in seeing Wu as irrelevant, the Examiner stated:

> Wu provides a single example of a peptide boronic acid [sic] is not stable in alkaline conditions which are required for production of the salts of the instant invention. According to the applicant one of ordinary skill in the art would not be motivated to make base addition salt [sic] of boronic acids in view of the teachings of Wu et al. This argument is not found persuasive. Wu only provides experimental data for a single compound that does not fall within the scope of the instant invention with a single base, NaOH. Adams on the other hand suggests making boronic acid salts that do fall within the scope of the instant invention and teaches using a variety of salts, not only the sodium salt.

Office Action at page 5.

Applicants respectfully point out that in making this statement, what the Examiner has apparently overlooked is the fact that the compound studied by Wu falls within the disclosure of Adams, and therefore would have been directly relevant to one of ordinary skill in the art who would have read Adams. Applicants respectfully submit that the Examiner cannot have it both ways -- either the entire disclosure of Adams is relevant to the present claims or none of it is relevant[1] -- and it is improper for the Examiner to read Adams so selectively as to read out the relevance of Wu, which clearly discloses an embodiment of the boropeptides disclosed in Adams to one of ordinary skill in the art.

To the extent that the Examiner believes that Adams is more relevant than Wu because Adams purportedly suggests making boronic acids salts that fall within the scope of the presently claimed invention, it is respectfully pointed out that independent claims 14 and 23 recite an imino acid, which is not disclosed in Adams. Independent claims 14 and 23 recite the structure:



(II)

where:

X is H or an amino-protecting group;

[1] *See* M.P.E.P. 2141.02, Part VI. ("Prior Art Must Be Considered In Its Entirety, Including Disclosures That Teach Away From The Claims").

aa^1 is an amino acid residue having a hydrocarbyl side chain containing no more than 20 carbon atoms and comprising at least one cyclic group having up to 13 carbon atoms;

aa^2 is an imino acid residue having from 4 to 6 ring members; and

R^1 is a group of the formula $-(CH_2)_s-Z$, where s is 2, 3 or 4 and Z is -OH, -OMe, -OEt or halogen.

In contrast to the presently claimed invention, Adams fails to disclose that the moiety corresponding to aa^2 is an imino acid. Indeed, in column 4 of Adams, in structure (1a), moiety R^2 is not permitted to be joined to peptide residue X^1. Hence, Adams fails to disclose or even suggest the presently claimed base addition salt.

The presently claimed invention provides pharmaceutically acceptable base addition salts of peptidyl boronic acids having the chemical structure recited in the claims. These peptidyl boronic acid base addition salts are useful as thrombin inhibitors. In order for a compound to be pharmaceutically useful as a thrombin inhibitor, it must have sufficient stability for an acceptable shelf life. *See* the Kennedy Declaration at ¶5. In the field of boronic acids, stability is a property which is deficient and therefore desired. *See* Wu at page 758; *see also* Gupta, WO 02/059130 (hereinafter "Gupta"), which is of record in the present application, at paragraphs [0004] and [0005]. As discussed in detail in the Supplemental Amendment and Reply filed on September 26, 2007, and in the Kennedy Declaration, Wu teaches away from making base addition salts of boronic acids.

At page 4 of the Office Action, the Examiner stated that "[o]ne of ordinary skill in the art would be motivated to produce various pharmaceutically acceptable salts in

order to achieve the desired properties of the pharmaceutical agent." However, the Examiner has failed to provide any evidence, apart from Davies, for the notion that one of ordinary skill in the art would have been motivated to make the base addition salts of the peptidyl boronic acids recited in the present claims. As discussed in the Kennedy Declaration, Davies is contradicted by the science relating to the boronic acid TRI 50c. Specifically, paragraph 35 of the Kennedy Declaration explains that Davies' assertion that the stability of an unstable acid could be improved by converting the acid into a salt of reduced solubility is contradicted by the facts relating to TRI 50c. Therefore, one of ordinary skill in the art would not have been motivated to make the presently claimed base addition salts.

The Examiner refers at page 4 of the Office Action to making "various pharmaceutically acceptable salts." The present application is directed not to "various" pharmaceutical salts, but is directed to base addition salts. The Examiner has failed to provide any evidence that one of ordinary skill in the art would have been led to make base addition salts of the peptidyl boronic acids recited in the pending claims that would be stable enough to be therapeutically useful.

Further evidence of the nonobviousness of the claimed invention is provided in the form of the Marsden Declaration filed herewith. Specifically, as Dr. Marsden discusses in his Declaration, boronic acids are recognized to be oxidatively unstable and to occur as heterogeneous mixtures with their anhydrides. *See* the Marsden Declaration at ¶ 5. In view of the instability of boronic acids, free boronic acids would not be a good choice for a drug substance. *See id.*

As Dr. Marsden explains, the most common technique for stabilizing a boronic acid is to combine the boronic acid with a strong Lewis base, for example, diethanolamine or fluoride. *See* the Marsden Declaration at ¶ 6. Another common method for stabilizing a boronic acid is to derivatize the boronic acid as an ester with a bulky diol, such as pinanediol. *See* the Marsden Declaration at ¶ 7.

Dr. Marsden also explains that the usual mechanism for boronic acid degradation is oxidation, and that the stabilization techniques he discusses in paragraph 6 of his Declaration work by forming tetravalent boron and blocking access to the boron atom by the oxidant species. *See* the Marsden Declaration at ¶ 8. Dr. Marsden also explains that bulky ester forming groups would seem to act by disfavoring formation of an adduct with the oxidant on steric grounds. *See id.*

In paragraph 9 of his Declaration, Dr. Marsden discusses work done on providing the drug Velcade[2] as a stable drug formulation as described in Wu and in Gupta. Wu shows that the use of strongly basic conditions leads to rapid decomposition of the boronic acid, presumably mediated by hydroperoxide anion. *See* the Marsden Declaration at ¶ 9. Gupta describes the stabilization of the Velcade free acid in the form of a mannitol ester. *Id.* According to Dr. Marsden, the advantages of the mannitol ester are that it prevents anhydride formation and provides a steric barrier to oxidation, and there may also be some stabilization by the action of further hydroxyl groups of mannitol as a Lewis base to complex the boron. *See id.*

[2] As shown in the package insert for Velcade (bortezomib) filed in the present application with the Kennedy Declaration on September 26, 2007, Velcade is a modified dipeptidyl boronic acid, and the product is supplied as a mannitol ester.

In paragraph 10 of his Declaration, Dr. Marsden explains that he has been asked to put himself in the shoes of a chemist, prior to the filing date of the present application, and tasked with stabilizing boronic acid TRI 50c or Rewinkel's boronic acid 21, taking into account the documents cited by the Examiner and the general knowledge of boronic acid chemistry. According to Dr. Marsden, his first thought would have been to use one of the conventional techniques to form a tetrahedral adduct. *See* the Marsden Declaration at ¶ 10. In particular he would have thought of making the diethanlolamine adduct. *See id.* This might have proved to be excessively stable, *i.e.*, too hard to cleave. *See id.* If that proved to be the case, the next logical thing would have been to put on a bulky ester forming group, *e.g.*, pinacol or pinanediol, or mannitol as proposed by Gupta. *See id.* Dr. Marsden explains that he would have discarded fluoride for toxicity reasons. *See* the Marsden Declaration at ¶ 11. Dr. Marsden also explains that it would not have occurred to him to convert TRI 50c or Rewinkel's compound 21 into a base addition salt as described in the present application. *See* the Marsden Declaration at ¶ 12. That is because he has never read of a boronic acid being isolated as a base addition salt. *See id.* In addition, to his knowledge, boronic acids are always sold either as the free acid (recognized to be an impure mixture), as an ester or less frequently as a trifluoroborate salt. *See id.* Dr. Marsden does not regard salt formation as described in Adams as an obvious way of isolating the compound, particularly for the reasons he provides in paragraph 13 of his Declaration. *See id.*

As Dr. Marsden further explains in paragraph 13 of his Declaration, hydroxides are used to activate boronic acids from transmetallation reactions. In these transmetallation reactions, a free boronic acid is combined with a transition metal and a

hydroxide base. *See id.* The hydroxide tetracoordinates with the boron, thus weakening the B-C bond and thereby promoting transfer of the organic moiety to the metal. *See id.* This is a relatively common procedure and Dr. Marsden would have asked himself why boronic acids are not sold as salts for use in the reaction. *See id.* In thinking of this, Dr. Marsden would have borne in mind that the presence of alkali activates peroxide by forming the hydroperoxide anion, as described in Wu and was well known to organoboron chemists. *See id.* The risk which alkali would present of causing degradation taken together with the observation that boronate salts were, to Dr. Marsden's knowledge, never sold, despite their apparent commercial attractiveness, would have biased him against making salts, even if that had occurred to him as an otherwise reasonable way forward. *See id.*

For these reasons, it would not have been obvious to Dr. Marsden to convert a peptidyl boronic acid such as TRI 50c or Rewinkel's compound 21 to a base addition salt for the purpose of making a pharmaceutical formulation. *See* the Marsden Declaration at ¶14. Similarly, Dr. Marsden would not have predicted that the salts would have the enhanced stability demonstrated by the data in examples 27 and 28 of the present application. *See id.* The improved stability came to him as an unexpected observation. *See id.* Therefore, the claimed base addition salt would not have been obvious over the cited art.

At page 6 of the Office Action, the Examiner stated:

> Applicant also argues and Dr. Kennedy declares that Rewinkel teaches an incorrect structure for compound 21 (Page 6 of the Remarks). The cited reference (Deadman et al.) in fact does not teach the free acid but rather an ester. One of ordinary skill would recognize that Rewinkel provides the active ingredient as boronic acid and

> Deadman provides the protected Boronic acid. With the teaching of Rewinkel and Adams one of ordinary skill in the art would be free to chose [sic] from either preparing the salt as Adams teaches, or preparing an Ester as Deadman teaches. The combination of Riwinkel [sic] and Adams is still sufficient to make a *prima facie* case for obviousness.

Dr. Marsden comments on Rewinkel's compound 21 in paragraphs 15-17 of his Declaration. As Dr. Marsden explains in paragraph 15 of his Declaration, Rewinkel states that it is describing the results obtained in four classes of fibrinogen-derived low molecular weight leads. In paragraph 2 of page 1054 of Rewinkel, it is stated that "To stress the uniqueness of the boronic acid class, researchers replaced the guanidine group with non-basic moieties like the meta-cyanophenyl in **20** and the methoxy propyl in **21** [48, 49]." *See* the Marsden Declaration at ¶ 15.

Dr. Marsden explains that in referring to compounds 20 and 21, Rewinkel is merely describing work previously published by researchers in references 48 and 49. *See* the Marsden Declaration at ¶ 16. Reference 49 is Lee and describes the *meta*-cyanophenyl containing compound 20, and reference 48 is Deadman and describes methoxypropyl-containing compound 21. *See id.* Rewinkel does not disclose the identity of the N-terminal group R of compound 21, but does disclose the tripeptide sequence Dpa-Pro-boroMpg, where Dpa is diphenylalanine, Pro is proline and boroMpg is boro-methoxypropylglycine. *See id.* The only such compound described as having been made in Deadman is compound 18, which is Z-D-Dpa-Pro-boroMpg-OPin (**18**), where Z is benzoyloxycarbonyl and -OPin designates the pinanediol ester. *See id.*

As Dr. Marsden explains in paragraph 17 of his Declaration, since compound 21 of Rewinkel is a compound disclosed in Deadman and the only compound of Deadman

having a matching tripeptide sequence is compound 18, Dr. Marsden concludes that compound 21 of Rewinkel must be the pinanediol ester 18 of Deadman, and not a free boronic acid as illustrated in Rewinkel. The free boronic acid would be the active species. *See* the Marsden Declaration at ¶17.

For the reasons discussed previously and herein, one ordinary skill in the art would not have thought to make a base addition salt of the peptidyl boronic free acid.

Accordingly, a *prima facie* case of obviousness cannot be established using the cited documents. However, even if a *prima facie* case of obviousness had been or could be established, the presently claimed invention provides unexpected results. At page 4 of the Office Action, the Examiner stated:

> In the absence of some unexpected properties for the base addition salts of [sic] organoboronic acids of the instantly claimed compounds, the invention is seen to be prima facie obvious in view of the prior art of record and the case law cited herein.

Applicants respectfully disagree. As Dr. Marsden explains in paragraph 14 of his Declaration, improved stability came to him as an unexpected observation. Therefore, the presently claimed invention would not have been suggested by the cited art.

Applicants respectfully request that this rejection be reconsidered and withdrawn.

III. The Rejection For Obviousness-Type Double Patenting

The Examiner has also rejected claims 1-23, 26-28, 30-55, 57 and 59-71 for non-statutory obviousness-type double patenting over claims 1-21, 23, 25, 50-56 and 71-73 of U.S. Patent No. 7,112,572. Applicants respectfully traverse this rejection. However, to the extent that this rejection is applied to the presently pending claims, Applicants

respectfully request that this rejection be held in abeyance until the Examiner has identified allowable subject matter in the present application. At such time, Applicants will consider filing a terminal disclaimer to obviate this rejection.

Conclusion

All of the stated grounds of rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider and withdraw all of the presently outstanding rejections.

Applicants believe that a full and complete reply has been made to the outstanding Office Action. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

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Date: July 30, 2008

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